CONCISE REVIEW: ABSORPTION AND TRANSPORT OF IRON

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SUMMARY: Iron is an essential element for humans like many other living organisms. Both insufficient and increased amounts of iron result in disease. In this concise review, absorption, transport, and cellular metabolism of iron will be discussed. Some related disorders are also mentioned in this review.

Key Words: Iron, anemia, ferrous.

ABSORPTION OF IRON

The first step of iron absorption is conversion of ferric iron (Fe^{+3}) to ferrous form (Fe^{+2}) by duedonal cytochrom b reductase. This step is essential, since duedonal metal transporter 1 (DMT1) allows only divalent metals (mostly iron, but also Cu, Pb, and Mn) through apical membrane of duedonal enterocytes. However, DMT1 is not the only molecule that facilitates transport of iron through enterocyte membrane. Heme carrier protein is another important molecule that transports iron within heme from apical surface into the enterocyte. In enterocytes and also in macrophages, substraction of iron from heme requires a multistep metabolic pathway. In this pathway, heme oxigenase 1 is a crucial enzyme (1,2).

Ferrous iron is transported from enterocyte to blood by means of ferroportin. Ferroportin takes place at basolateral surface of enterocytes and macrophage membranes. If total body iron is high, hepatic synthesis of hepcidin increases. Binding of hepcidin to ferroportin in its exterior segment causes internalization, ubiquitination and degradation of ferroportin. As a result, iron transfer to blood is decreased (3,4). Ferroportin, like DMT1, is permeable only to ferrous iron. On the other hand, iron has to be in ferric form to be bound by transferrin. Therefore, oxidation of ferrous iron (Fe^{+2}) to the ferric (Fe^{+3}) form by hephaestin is necessary. Ceruloplasmin is a hephaestin homolog settled on macrophage membranes nearby ferroportin, doing the same work with hephaestin. In summary, ferrous iron exported from enterocytes is oxidized by hephaestin, and ferrous iron exported from macrophages is oxidized by ceruloplasmin in the same manner (5).

TRANSPORT OF IRON

Transferrin (Tf) is the major protein that binds and delivers iron to tissues. Each Tf molecule can transport 2 ferrous iron molecules (6). Conformation of the binding site is suitable with ferric iron in a delicate manner (7). Transferrin binds to one of the transferrin receptor (TfR) on cell membrane; TfR1 or TfR2 (8). Transferrin receptor 1 is expressed in all tissues except mature erythrocytes. It is an important molecule in embryogen-

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Table: Some iron related disorders.

Molecule	Inheritance	Function	Disease	Reference
DMT1	Autosomal recessive	Transport of divalent metals, mainly iron	Hypochrom microcytic anemia at birth, Small for gestational age, hepatic iron deposition	24
Heme oxigenase 1	Autosomal recessive	Substraction of iron from heme	Persistent intravascular hemolysis, hepatic and renal iron deposition	25
Ceruloplasmin	Autosomal recessive	Oxidization of ferrous iron exported from macrophages	Aceruloplasminemia, iron deposition in brain, liver and pancreas, retinal degeneration, ataxia, demans, movement disorder	26
Ferroportin	Autosomal dominant	Transport of iron from enterocytes or macrophages to blood	Ferroportin disease (Hereditary hemochromathosis Type 4)	27
HFE	Autosomal recessive	Controls transition of iron from endosome to cytoplasma	HFE (Hereditary hemochromathosis Type 1)	
Hemojuvelin	Autosomal recessive	Suppresses hepcidin levels by means of bone morphogenetic proteins	Juvenile hemochromathosis (Hereditary hemochromathosis Type 2a)	
Hepcidin	Autosomal recessive	Induces internalization, ubiquitination and degradation of ferroportin via Janus Kinase 2	Juvenile hemochromathosis (Hereditary hemochromathosis Type 2b)	
Transferrin receptor 2	Autosomal recessive	Transports Tf through the cell membrane especially in hepatocytes, regulates hepcidin expression	Hereditary hemochromathosis Type 3 (HH3)	
TMPRSS6 (matriptase 2)	Autosomal recessive	Supresses hepcidin levels by means of bone morphogenetic protein 6	IRIDA (iron resistant iron deficiency anemia)	28
Transferrin	Autosomal recessive	Transports iron from enterocyte to cells	Hereditary atransferrinemia, Hypochrom microcytic anemia, iron deposition in liver, pancreas, heart, and endocrine organs	29
Ferritin	Autosomal recessive	Reacts with Fe+2 and facilitates its oxidation to ferrihydrite in order to prevent oxidative damage	1.Hereditary hyperferritinemia cataract syndrome 2. Neuroferritinopathy	30, 31
Frataxin	Autosomal recessive	Bifunctional mitochondrial protein that acts as a chaperone or stores iron due to cellular iron levels	Friedreich ataxia	32
ATP-Binding Cassette, Subfamily B, Member 7 (ABCB7)	X-linked recessive	Transports ISCs to cytoplasma, a putative role in heme synthesis is also suggested	X-linked sideroblastic anemia/ataxia	33
Delta aminolevulinic acid synthase	X-linked recessive	Rate limiting enzyme in heme synthesis in erythrocytes	X-linked sideroblastic anemia	34
Glutaredoxin 5	Autosomal recessive	Important enzyme in iron sulfur cluster synthesis within mitochondria	Pyridoxine-unresponsive sideroblastic anemia, iron deposition in liver,	35
Iron-sulfur cluster scaffold	Autosomal recessive	Assembly of Fe-S clusters	Myopathy associated with ISCU1 defect	36
BCS1L	Autosomal recessive	A chaperone that facilitates insertion of Rieske Fe/S protein into mitochondrial respiratory chain complex III	Gracile syndrome (Growth retardation, a.a.uria, cholestasis, iron overload, lactic acidosis, early death)	37

esis. Transferrin receptor 1-knockout embryos do not survive due to defective erythropoiesis and neurological maldevelopment (9). However, other tissues in body are not affected in the absence of TfR1 which indicates additional mechanism(s) for iron transport in these cells. Transferrin receptor 2 is primarily expressed in the liver (10). Although protein structures of TfR1 and TfR2 have a high degree of homology, their functions and regulation are not the same. Expression of TfR1 is tightly regulated by cellular iron levels through HFE (hereditary hemochromathosis) protein. However, cellular iron levels have no effect on the regulation of TfR2. TfR2 senses the body iron status by sensing the transferrin saturation and regulates hepcidin expression properly (11).

After binding of diferric Tf to TfR, Tf/TfR complex on the clathrin-coated cell membrane is internalized by a receptor-mediated endocytosis. Within endosomes, acidification process by means of an ATPase proton pump (pH 5.5-6) helps to dissociate iron from Tf. A protein called STEAP3 (Six-Transmembrane Epithelial Antigen of Prostate 3) has been shown to convert Fe^{+3} to Fe^{+2} in erythroid precursor cells (12). This convertion is necessary since DMT1 allows only divalent metals from endosome to cytoplasm as in the enterocytes. The endosome containing Tf and TfR fuses back to the plasma membrane after release of iron. Non-transferrin-bound iron can be derived from plasma only by hepatocytes.

CELLULAR DISTRIBUTION OF IRON

In cells, iron can be stored within ferritin or it can be used for cellular reactions. A newly discovered protein, PCBP1 (Poly r(C)-Binding Protein 1), has been reported to transfer iron from endosome to ferritin (13). Ferritins are spherical structures that accommodate large amounts of iron in a safe, soluble and bioavailable form. It consists of two subunits; namely H and L. Ratio of H to L subunits in ferritin molecule is varied depending on the tissue type and also physiologic status of a given cell. L type is predominant in liver and spleen whereas H type is predominant in heart and kidney. Ferritin reacts with Fe^{+2} and facilitates its oxidation to ferrihydrite. This is a critical step in order to prevent oxidative damage that could be caused by free iron within cytoplasm (14).

Like many other molecules, iron crosses the mitochondrial outer membrane via porin (15). The inner membrane contains mitoferrin, a special carrier for iron. Heme synthesis and iron sulfur cluster (ISC; also known as 4Fe-4S clusters) biogenesis are two important iron related reactions occur within mitochondria (16). Within mitochondrial matrix, both frataxin and mitochondrial ferritin can store iron. Frataxin is a bifunctional protein (17). When mitochondrial iron is limited it works as a Fe^{+2} chaperone. When iron is in excess, it works as a storage compartment forming ferrihydrite like cytoplasmic ferritin.

Iron sulfur clusters are cofactors in several reactions such as electron transport, Krebs cycle, regulation of gene expression, and redox reactions (16). These clusters have also been shown in cytoplasm within iron response protein 1 (IRP1) and in nucleus within an enzyme which is involved in base excision repair. Transport of ISC to cytoplasma happens by means of a spesific carrier, ABCB7 (ATP-Binding Cassette, Subfamily B, Member 7) (18). The other important molecule synthesized in mitochondrion is heme. Out of 8 steps in heme biosynthesis, 4 steps take place within mitochondria. The first and rate-limiting step of the pathway is condensation of succynil CoA and glycine to delta-aminolevulinate catalyzed by delta-aminolevulinate synthase (ALAS). There are 2 types of ALAS; ALAS1 and ALAS2 (erythroid ALAS). Erythroid cells rely on ALAS2 for hemoglobin synthesis.

CONTROL OF IRON ABSORPTION

Since excess iron is toxic for cells, there are several mechanisms to control iron level. One of these mechanisms control absorption of iron at enterocyte. Hepcidin and ferroportin are key proteins at this level. During transport of iron HFE protein is very important to control transition of iron from endosome to cytoplasma. Above all, since the need of iron differs in different cells, control of iron uptake at cellular level is very important.

Hepcidin, one of the key regulators of iron in body, is mainly produced by liver. There are several molecules as well as body iron levels that control hepcidin level (19). Iron overload in body induces hepcidin levels. On the contrary, iron deficiency, hypoxia or erythroid expansion reduces hepcidin expression. During low iron conditions in body, increased soluble hemojuvelin and TMPRSS6 (matriptase 2) activity suppresses hepcidin levels. Erythropoietin, hypoxia inducible factor-1 (HIF1) and GDF15, a molecule found in thalassemic patients' sera, also cause suppression in hepcidin levels.

Iron uptake is separately regulated in each cell according to the need of iron in a given cell. This regulation is not adjusted by iron regulators in body such as hepcidin or GDF15. There are two important molecules in cellular iron metabolism; iron responsive proteins (IRP1 and IRP2) and iron responsive element (IRE) (20,21). When cellular iron is depleted, IRP1 and IRP2 bind to IREs of a number of molecules. These molecules are related to iron uptake (TfR1, DMT1), utilization [5-aminolevulinate synthase (ALAS1) and erythroid ALAS (ALAS2)], storage (H- and L-ferritin) or export (ferroportin). Very recent studies disclosed that at least two cell cycle-related molecules, MRKC (myotonic dystrophy kinase-related Cdc42-binding kinase) and CDC14A (cell division cycle14A), also bear IREs in their mRNA at 3' untranslated region (UTR). In order to maintain optimum iron levels in each cell, synthesis of iron related proteins is regulated by IRPs. IRE/IRP interaction results in stabilization or translational repression of mRNA determined by the location of IRE (22). When iron level is low within a cell, synthesis of both IRP1 and IRP2 increases. Interaction of IRPs with IREs in the 3' UTR of mRNA results in stabilization. Stabilization of mRNA results in increased expression of molecules related with uptake of iron such as TfR1 and DMT1. In the meantime, interaction of IRPs with IREs in the 5' UTR of mRNA results in translational repression, the expression of molecules related with deposition and metabolism of iron such as ferritin, ferroportin, and ALAS2 are supressed. When cellular iron level is high, both IRP1 and IRP2 lose their affinity to IRE. In this circumstance, reciprocal reactions occur in the opposite manner; expression of molecules related with uptake of iron such as TfR1 and DMT1 decrease and expression of molecules related with deposition and metabolism of iron such as ferritin, ferroportin, and ALAS2 increase. IRP1 is a bifunctional protein. It binds iron-sulfur clusters (4Fe-4S) when intracellular iron is high and functions as aconitase that has no IRE related function. On the other hand, high intracellular iron levels do not cause a conformational change that rather causes degradation of IRP2. HFE protein is another molecule that has an influence on cellular iron levels. In normal conditions, HFE protein decreases the affinity of TfR1 for Tf by a magnitude of 10 to 50 (23). Mutations in HFE gene may alter the iron absorbtion and cause hemochromathosis phenotype.

In conclusion, iron metabolism is a rapidly expanding field that facilitates knowledge in many clinical disciplines. To be up-to-date in this field is essential for clinicians as well as scientists in order to understand pathophysiology of certain diseases.

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